Specialty Conference

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Rickets

WILLIAM L. NYHAN, MD, PH D:* Rickets is one of the classic problems in pediatrics. It illustrates very clearly the close interaction between the processes of growth and development and disordered physiology that make disease special in the pediatric age group. The discovery of vitamin D and its widespread application throughout the world was a major advance in public health which converted a very common disorder into a rarity. Nevertheless, it is not true that we see more patients with vitamin D-resistant rickets than with vitamin D-deficiency rickets. The classic disorder is still with us. In this conference we shall review some of the classic findings and some of the new information in this area. The first patient will be presented by Mr. Gersh.

ELLIOTT S. GERSH:† Case 1. A 2-year-old black boy was referred for evaluation of bilateral bowed legs. When the patient was an infant he had been noted to be bowlegged. However, several other members of the family were mildly bowlegged and this was not thought to be significant. The bowing became more pronounced when the patient began to walk at 13 months of age. He was seen at the age of 19 months at Children's Orthopedic Hospital in Seattle where findings on x-ray studies were suggestive of rickets.

The patient was the product of a normal pregnancy and delivery. The birth weight was 2,667 grams (5 lb 14 oz). There were no significant problems or illnesses. The infant was breast fed until he was 17 months old, but he also ate solid foods and had a good appetite. The history was that he was given vitamins A, D and C in the form of Tri-Vi-Sol® from 6 to 12 months of age.

The patient's father, three paternal uncles and a 5-year-old brother had mildly bowed legs. The father was examined and the findings were minimal.

On physical examination the patient was found to be healthy and active. The only abnormal findings were the bilateral tibial bowing and a height of 81.3 cm (32 in). This was a height age of 18 months at a chronological age of 27 months. Laboratory studies in Seattle had shown the concentrations of calcium, phosphate, electrolytes and blood urea nitrogen (BUN) as well as an amino acid screen of the urine to be normal. The alkaline phosphatase was slightly elevated. On x-ray films, signs of active rickets as well as the old deformities were seen (Figure 1). The patient was felt to have vitamin D deficiency. He was treated with 10,000 units of vitamin D daily. On repeat x-ray studies made during a six month period, progressive healing was noted.

DORIS TRAUNER, MD:‡ Case 2. A 2-month-old black boy was admitted because of jitteriness and left-sided jerking. The patient was well until the day of admission when three brief episodes of

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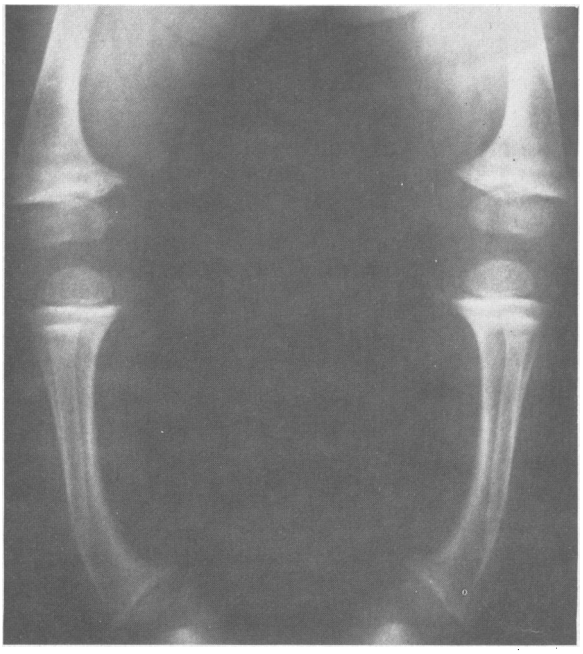

Figure 1.—(Case 1) Rickets already healing at the time of the first radiograph continued to heal progressively over a period of six months. There are fractures of the distal tibias. Bowing deformity of tibias is prominent but the fibulas and femurs are also bowed. This bowing was still present after six months.

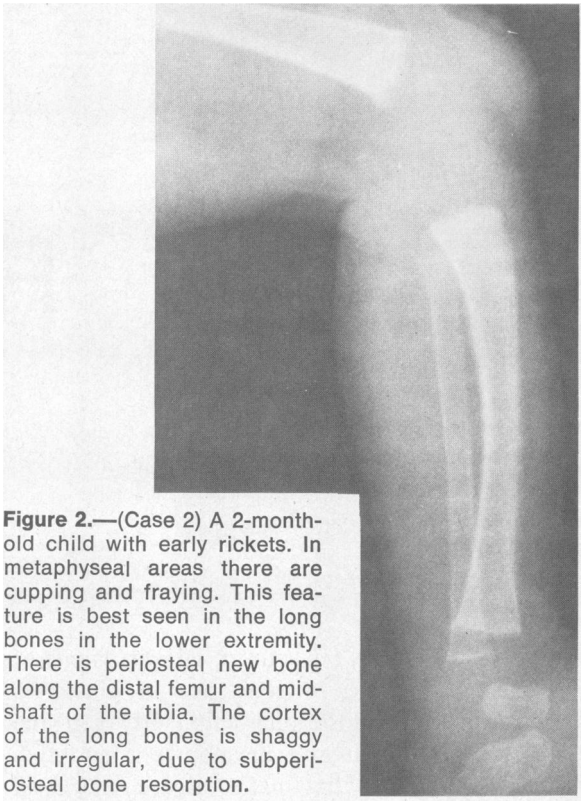

Figure 2.—(Case 2) A 2-month-old child with early rickets. In metaphyseal areas there are cupping and fraying. This feature is best seen in the long bones in the lower extremity. There is periosteal new bone along the distal femur and mid-shaft of the tibia. The cortex of the long bones is shaggy and irregular, due to subperiosteal bone resorption.

clonic movements of the left arm and leg occurred which lasted approximately 3 to 4 seconds. The child was brought to another hospital where on lumbar puncture cerebrospinal fluid was found to be normal. Phenobarbital (Nembutal®) was given and the patient was transferred to University Hospital.

The patient was born at 36 weeks gestation by cesarean section because of cephalopelvic disproportion and two previous sections. Birth weight was 2,213 grams (4 lb 14 oz). The baby was in hospital for seven days for temperature instability and inability to gain weight. The baby was fed Enfamil® plus iron approximately 20 to 30 oz per day. Baby cereal was started at 2 weeks of age, and vitamins A, D, C and fluoride (Tri-Vi-Flor®) were started at 6 weeks.

Family history and review of systems were noncontributory.

On physical examination, the infant was found to be well-developed but lethargic. Body weight was 3,376 grams (7 lb 7 oz). The fontanelle was not tense. The pupils were equal and reactive to light, and the fundi were benign. A grade III/VI holosystolic murmur heard at the left sternal border radiated to the axilla and pulmonic area. The baby had a poor suck and Moro reflex. The deep tendon reflexes were 2+ and equal bilaterally. There was a pronounced and sustained clonus. Chvostek and Trousseau signs were positive.

Initial laboratory studies gave the following values: hemoglobin, 9.8 grams per 100 ml; hematocrit reading, 28 percent; leukocyte count, 10,400 per cu mm with 35 segmental polymorphonuclear cells, 4 band forms, 56 lymphocytes and 5 monocytes. The serum concentration of calcium was 5.4, magnesium 1.9 and phosphate 4.8 mg per 100 ml. The alkaline phosphatase value was 16 units (normal adult value 2 to 5 units). Electrolytes were normal, as were the total protein, glucose and BUN levels. The urinary calcium level was 2.7 mg per 100 ml. X-ray studies showed early rickets to be present (Figure 2).

The patient was immediately treated with 400 mg of calcium gluconate given intravenously. For approximately one week the infusion was continued and the dose was increased to 1,500 mg of elemental calcium per day in order to maintain normocalcemia. Gradually he could be weaned to a regimen of 600 mg of calcium and 1,000 units of vitamin D given orally. Two months later, the serum calcium level was 9.7 and the phosphorus level was 6.1 mg per 100 ml. The

patient was receiving 2 tsp three times a day of glubionate calcium (Neocalglucon®) and 1,000 units of vitamin D per day. Findings on x-ray studies of the wrists showed healing of the rickets.

Case 3. A 4-month-old white boy was referred to University Hospital because of left-sided seizures which had begun at three o'clock that morning.

The patient was born after approximately 28 weeks of gestation to a gravida 2, para 2, 40-year-old woman who had had two episodes of vaginal bleeding before the delivery. The birth weight was 1,007 grams (2 lbs 12 oz) and the infant was kept in a nursery for approximately three months. During that time his problems were hyperbilirubinemia with values up to 15 mg per 100 ml, which was considered to constitute physiological jaundice, and intermittent apnea responsive to stimulation which lasted into the fourth week. He was discharged one month before this admission weighing 2,156 grams (4 lbs 12 oz). He did well until the morning of admission when a left-sided focal seizure occurred which lasted approximately half an hour. A lumbar puncture carried out in a physician's office showed 6 mononuclear cells. Several left-sided seizures occurred in the office, each lasting one to two minutes. Treatment was carried out with paraldehyde, three times, and with phenobarbital. The infant was then transferred to University Hospital.

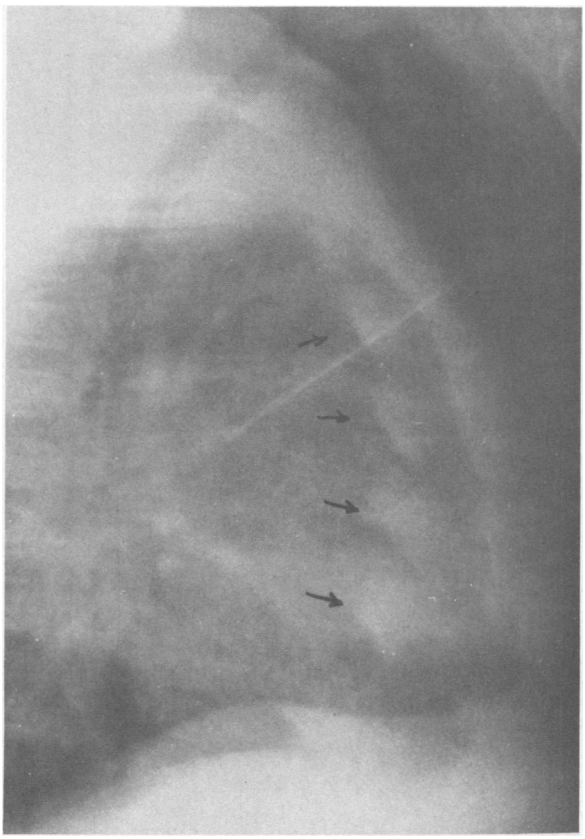

Figure 3.—(Case 3) A lateral radiograph of the chest showed accumulations of poorly-mineralized osteoid at the costochondral junctions, producing the classic "rachitic rosary" which was readily apparent on physical examination.

On arrival he was awake, but lethargic. He held his head in a slightly opisthotnoic position. He had infrequent, brief left focal seizures involving the left arm and the mouth.

The feeding history was pertinent in that he had been receiving breast milk and bananas. In the nursery he had been fed Enfamil for one month, and he was breast fed after that. He had received no vitamin supplements. He had had bilateral inguinal hernias and an umbilical hernia. His past history was otherwise noncontributory, as was the family history.

On physical examination, head circumference was found to be 39 cm, which was less than the third percentile for 4 months of age, but at the 90th percentile for 1 month of age, which was his age from the end of a normal gestation. The anterior fontanelle was large and full, and a widely spread metopic suture came down to his nose. There were a 1.5 cm umbilical hernia, and bilateral inguinal hernias. Head control was poor but he had a good suck, a full Moro reflex, good grasp and a positive stepping response.

Results of laboratory studies showed the presence of anemia with a hemoglobin value of 8.1 grams per 100 ml, a hematocrit reading of 24 percent and a reticulocyte count of 2 percent. Serum levels of electrolytes, glucose, BUN and creatinine were normal. The alkaline phosphatase value was 44 units (normal adult value 2 to 5 units). The serum concentration of calcium was 6.1, magnesium 2.0 and phosphate 5.2 mg per 100 ml. On an electrocardiogram, a prolonged QT interval was noted which was compatible with hypocalcemia. Electroencephalographic findings showed dysrhythmia grade III with minimal generalized slowing and generalized spiking in the right temporal region. Right upper lobe and right middle lobe infiltrates were seen on an x-ray film of the chest. At the costochondral junction, florid rickets was noted (Figure 3). On x-ray films of the skull, a profound lack of ossification in the calvarium was noted. Diploic sinuses were defin-

able only in the fontanelle and occipital regions. The entire base of the skull was poorly ossified.

The infant was treated with parenterally given antibiotics for the pneumonia and parenterally and orally administered calcium to stop the seizures and to correct the hypocalcemia. There was no recurrence of seizures. On supplementation with 400 units of orally given vitamin D per day, the serum concentration of calcium returned to normal levels. Two weeks after vitamin D therapy was started, the serum level of calcium was 9.4 mg per 100 ml. Two months later the value was 10.6 mg per 100 ml and the phosphate was 7.5 mg per 100 ml. On supplementation with iron, given orally, the reticulocyte count rose and the hematocrit reading returned toward normal levels.

MICHAEL WELLER, MD:* Using the three cases presented and some others, the radiologic findings in rickets will be reviewed, as well as the physiology responsible for producing the classical radiologic pattern.

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Figures 4 and 5 provide an example in which the rickets was considerably more florid than in the cases presented. It serves as a classical model. There is pronounced deossification of all the long bones. In addition, in the metaphyseal regions of the long bones cupping and fraying are seen to be present (Figure 4). The growth plates were considerably widened. In the metaphyses, normally the area of greatest density—the zone of provisional calcification—is replaced by a zone of lucency due to the absence of fully mineralized cartilage and bone.

In the first few weeks of the rachitic process, all that one may see radiologically is generalized rarefaction of bone. Soon, the normal progression of endochondral ossification slows and, as cartilage cells in the growth plate mature and begin degenerating, calcium is no longer available for deposition in the zone of provisional calcification. Large amounts of degenerating cartilage and immature, unossified osteoid accumulate, resulting in widening of the normally radiolucent growth plate. Because the process is not uniform, a

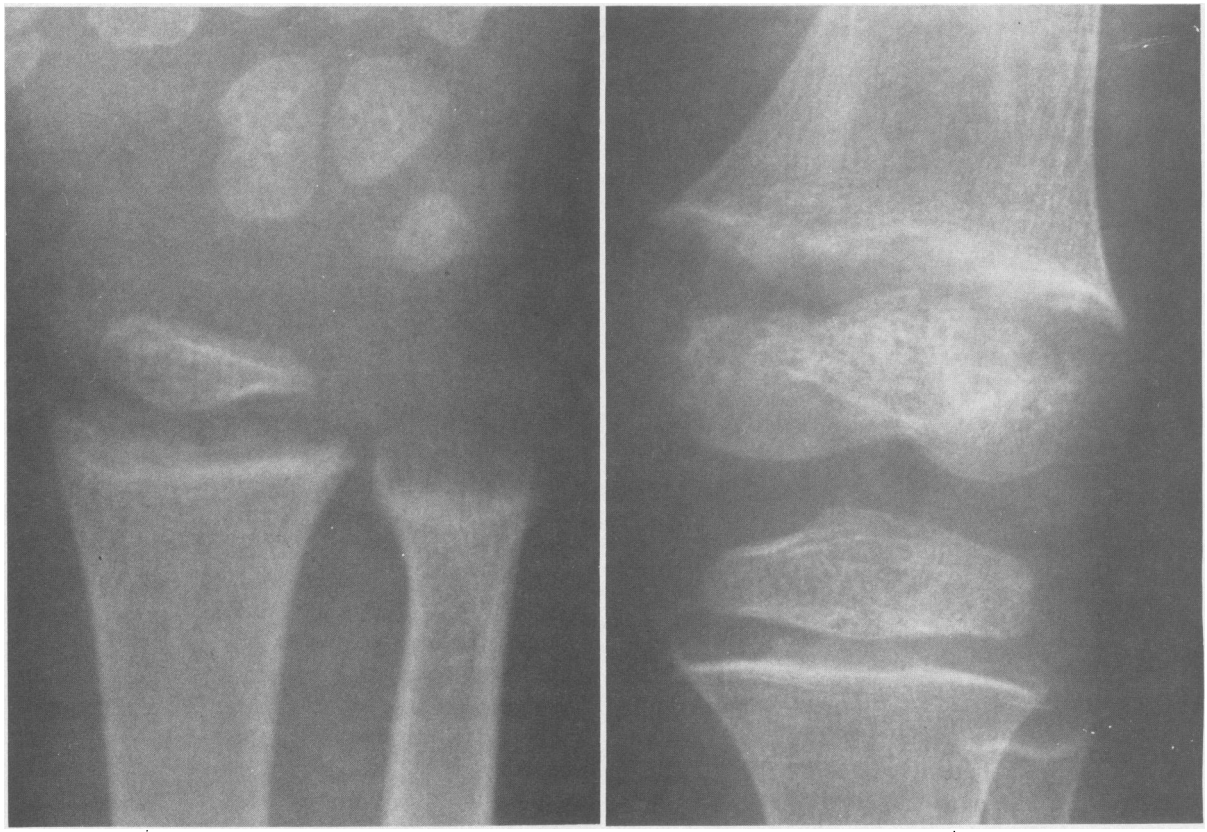

Figure 4.—Dietary rickets. In the metaphyseal areas at the wrist and knee there is widening of the growth plates with loss of normal density in the zone of provisional calcification. The process is irregular, leading to a frayed appearance. Cupping is present uniformly, but most pronounced in the distal ulna and proximal fibula.

"frayed" appearance of the metaphysis results. "Cupping" is due to continuing *periosteal* new bone formation at the periphery of the metaphysis just below the growth plate, which begins to surround the bulky osteoid accumulating in this area.

Cupping is seen best in the distal ulna, tibia and fibula, and at the distal radius only quite late in the disease. At times, the bulky knobs of poorly mineralized osteoid in the metaphyses cast soft tissue density on the radiograph. These collections are responsible for the palpable swollen joints and costochondral junctions (the "rachitic rosary").

Longitudinal growth of bone is accomplished by the process of endochondral bone formation. The periosteum is also capable of bone production. This latter process usually continues even after endochondral bone formation ceases, at least for a while. This may be manifest as lamina of periosteal new bone. Finally, periosteal new bone formation ceases also, and subperiosteal bone *resorption* begins, giving the entire bony diaphysis a finely irregular, or shaggy, appearance.

With therapy, through the direct action of vitamin D, circulating calcium and phosphorus are incorporated into the accumulating immature osteoid, and mature bone is formed. Radiologically, this results in the reestablishment of a new dense zone of provisional calcification, in a location where it would have been, had rickets not supervened (Figure 5). The lucency of the radiologically widened growth plate then begins to fill in gradually, the fraying and cupping are gradually remodeled, and the normal smooth tapered contours restored. The zone of lucency immediately shaftward from the *new* dense zone of provisional calcification may be reminiscent of leukemia, unless one notices the residual cupping and fraying, and is aware of the clinical history.

Bowing of the lower extremities may occur because of loss of the structural integrity of bone (Figure 1). This usually resolves in time with treatment in dietary rickets. Residual bowing is common in renal rickets. In the first patient, the 2-year-old child described this morning, radiographs showed progressive healing of the rickets over several months after the initiation of vitamin D therapy (Figure 1). The bowing was still prominent after six months.

The second patient described this morning was a 2-month-old child who presented with seizures. Radiographs of the skull provide the first evidence of profound deossification. Examination of the long bones confirms this and shows the characteristic cupping and fraying in the metaphyseal areas. This is most pronounced in the upper extremities

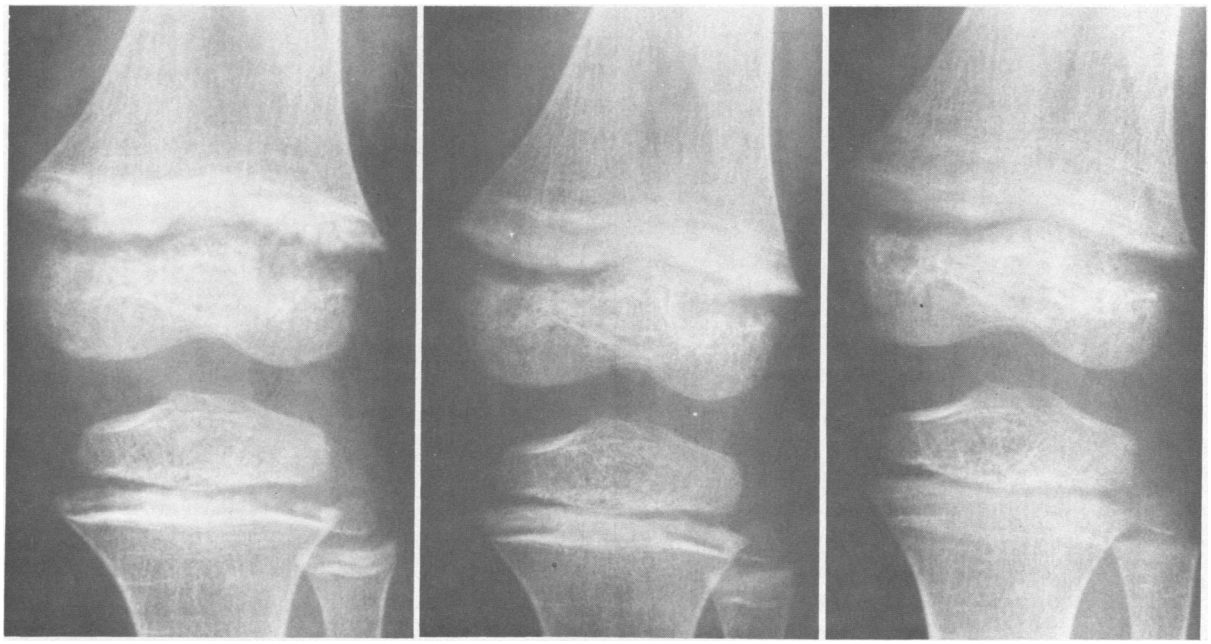

Figure 5.—Sequential healing of rickets following treatment with Vitamin D. (Same patient as in Figure 4.) These changes occurred over a period of four months. There is progressive restitution of the metaphysis with initial deposition of mineral closest to the epiphysis. The lucent zone in the metaphysis gradually fills in and disappears with continued healing.

in the distal ulnas. In the lower extremity it is prominent in the tibias, and fibulas (Figure 2). With therapy, the zone of provisional calcification begins to regain its original density and periosteal new bone formation blends with the cortex of the diaphysis.

The third patient, a 4-month-old infant, also presented with seizures, and radiographs show profound lack of bone in the calvarium, even in the petrous portions of the temporal bones, normally the most dense area in the skull of the infant. A large amount of unmineralized immature osteoid is present at the costochondral junctions, producing a rachitic rosary (Figure 3). The long bones show cortical thinning and irregularity, in addition to rachitic metaphyseal changes. There is irregularity in the metaphyses, well shown in the distal femur, proximal and distal tibia, and fibula. Cupping and fraying are most obvious in the distal tibia and fibula.

A final example of severe rickets is noted in twin chimpanzees from the San Diego Zoo (Figure 6). Changes are present that are identical to those described in the children presented this morning.

Vitamin deficiencies are rare today. Many food products contain vitamin supplements. The severe changes of rickets are seldom seen, and often the initial radiographs of a patient show evidence of partial, although insufficient bony response to treatment.

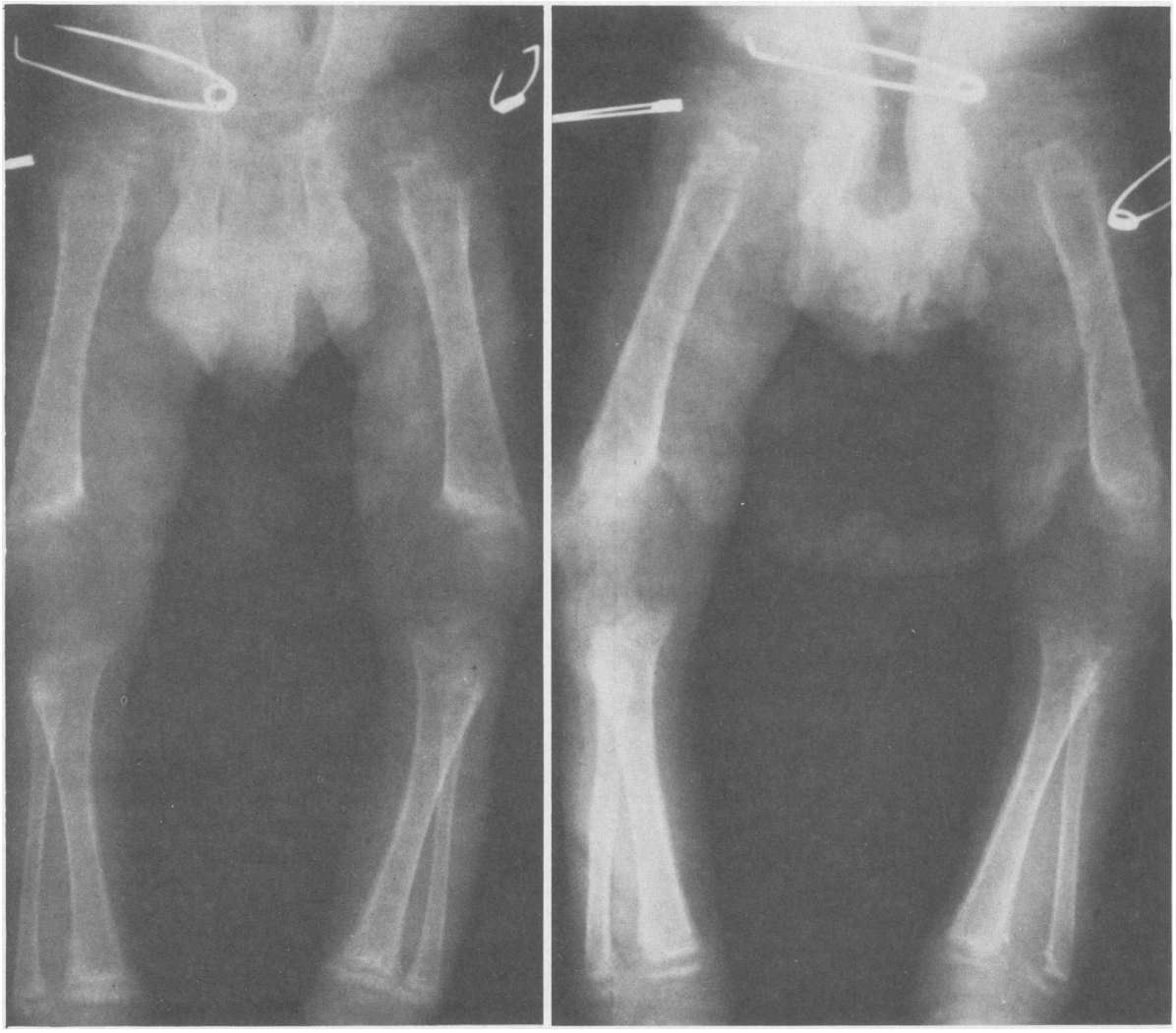

Figure 6.—Twin chimpanzees with rickets. Metaphyseal cupping and flaring, widened growth plates, periosteal new bone and cortical thinning are present. In contradistinction to humans, in chimpanzees similar changes develop in both epiphyses and metaphyses.

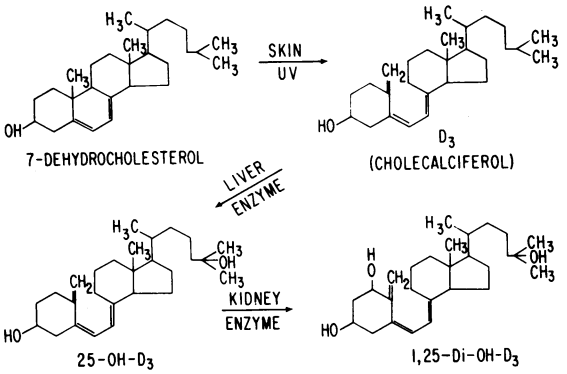

Figure 7.—The conversion of 7-dehydrocholesterol to its metabolites with vitamin D biological activity.

JERRY SCHNEIDER, MD:* I would like to begin with some comments about vitamin D and nutritional rickets. We should ask whether vitamin D is really a vitamin. I would like to suggest that it is not. It was named vitamin D because it was the fourth unidentified nutrient to be discovered.[1] Analysis of the structure (Figure 7) of the natural D vitamin, cholecalciferol, that we all make in our skin indicates that it is really a steroid and it is appropriate to think of it as such.

The history of vitamin D and rickets is fascinating.[1-4] Park's paper is very good. We do not know much more, from a clinical point of view today than he did 50 years ago.[2] Loomis has written two articles that deal with the history of vitamin D.[3,4] One in *Scientific American*[4] described the scientific arguments of investigators who thought rickets was a nutritional disease and those who thought it was environmental. Park felt that we should not think of rickets as a vitamin deficiency disease in the sense of beri beri and scurvy, but as an endocrine disease such as diabetes. Others have used thyroxin as an analogy. Cholecalciferol is produced in the skin just as thyroxin is produced in the thyroid. All of us have 7-dehydrocholesterol in our skin (Figure 7). Ultraviolet irradiation from the sun converts this in the skin to what is called vitamin D_3 or cholecalciferol. Only sunlight is needed to avoid rickets. Loomis considered rickets the first disease of air pollution.[3,4] Areas in which rickets first became prominent in Northern Europe were the areas in which soft coal was first used. The first clinical descriptions of rickets coincided very well with the introduction of soft coal.

Dr. Weller pointed out significant findings on x-ray films of two monkeys. Some pertinent studies were done at the turn of the century in London zoos. Animals that were fed a perfectly good diet in London zoos developed rickets, whereas their siblings, fed the exact diet in small zoos in nonindustrial areas of England did not. Loomis compared the distribution of skin pigment in various areas of the world with the availability of ultraviolet radiation from sunlight.[3,4] He proposed that lightly pigmented skin evolved in order to allow enough cholecalciferol production to prevent rickets. Some exceptions to the rule are easily explained. For instance, the Eskimos tend to have dark complexions, but live on a diet of fish which is rich in vitamin D. Fish are the only vertebrates that can make vitamin D without ultraviolet radiation.

It is humbling to read the history of cod liver oil. For many years leading physicians refused to believe that it had healing properties. Another interesting question is how people who lived in Northern Europe in areas without air pollution, but too cold to allow much exposure to sunlight in winter months, avoided rickets before widespread dietary supplementation with cod liver oil. The vitamin D that can be synthesized by a square centimeter of skin has been calculated, assuming the skin is very light in color so the ultraviolet light is not filtered out. A square centimeter of skin can make 18 units of vitamin D in three hours. Scandinavian mothers have known for hundreds of years that it is important to put their children outside each day for a few hours to get some fresh air and sunshine. These children are completely bundled on cold days, but their nice pink cheeks are exposed to the sunlight and you can calculate the square centimeters of skin exposed and find that in three hours about 400 units of vitamin D is produced. In the production of clinical rickets an absence of sunlight is a requirement. Linear growth of bone is also required to produce rickets. If a patient is very poorly nourished and not growing, rickets will not occur.

An excellent reference source on clinical rickets is the chapter by Harrison in Brennemann's *Practice of Pediatrics*.[5] It is relevant to the last two cases presented today to note what Harrison[5] wrote at least ten years ago:

> "Vitamin D deficiency may be apparent by 2 to 3 months of age particularly in prematurely born infants. The important finding at this stage is often hypocalcemia with only moderate reduction of serum phosphorus levels. Since the

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normal serum phosphorus concentration in the premature infant at this age is so high, a serum phosphorus level of 5 mg/100 ml may represent a relative hypophosphatemia."

This statement almost perfectly describes the third patient. Many physicians confronted with such an infant would feel that a serum phosphorus concentration of 5.2 mg per 100 ml was too high to permit a diagnosis of rickets since in a typical case of rickets the concentration would be under 4 mg per 100 ml. However, the normal serum phosphorus level in a 4-month-old infant is 6.4. In this infant, hypophosphatemia certainly was present.

In children with rickets there classically is a low serum concentration of phosphorus. The calcium level may be normal, or perhaps slightly low. In these children, however, there is very little calcium reserve. It is not possible in them for calcium to be mobilized from bones as quickly as in normal children; so their calcium balance is very precarious and they can easily be thrown into a situation in which the serum calcium rapidly decreases. This is often precipitated by infection. A few days of poor eating may cause the body to mobilize phosphorus precipitating some of the calcium and quickly lowering the serum calcium to a concentration that may cause tetany.

When I first saw the infant in the second case presented this morning, an article had just appeared in the *Journal of Pediatrics* by Lewis and co-workers.[6] They had specifically examined premature infants for rickets who were not given vitamin D. Their reasoning was that 400 units of the vitamin per quart of formula was only adequate if the infant actually took a quart of formula per day. Premature infants often take much less and, consequently, they get much less vitamin D. It has been known for many years that premature infants are especially susceptible to rickets. At one time doses quite a bit higher than 400 units a day were employed but I think most neonatologists now accept 400 units a day as sufficient. It is important that a premature infant actually get 400 units a day. Therefore it is wise to give 400 units a day of vitamin D as a supplement apart from the formula.

The treatment of rickets is somewhat controversial. The questions are how much vitamin D and how much calcium to give. Harrison[5] has been an advocate of a large push of vitamin D, amounting to 600,000 units of vitamin D administered as 100,000 units of D_2 orally every two hours for six doses. If nutritional rickets is present there should be a clinical response within one week and response noticeable on x-ray studies within two weeks. The rapid mobilization of calcium also protects against hypocalcemia. If no response is seen in two weeks, perhaps because of infection or steatorrhea, the dose is repeated. No more vitamin D is given for three months. Harrison has stated that he has never seen hypercalcemia following this form of treatment and that patients with vitamin D resistant rickets will not respond.[5] Other physicians never give this large a dose and prefer to give a few thousand units per day until they are sure of correction of the rickets. I like to employ large doses of vitamin D in a young infant with hypocalcemia tetany. It is very difficult in these infants to raise the calcium level quickly. A large dose of vitamin D may mobilize calcium rapidly and shorten the time in which parenteral calcium is needed.

The differential diagnosis of rickets may be extensive. If we consider the cases presented, there is little else but nutritional rickets that the infants in the last two cases could have had. We always think of vitamin D resistant rickets but rickets usually does not appear in these children until after 6 months of age, and they are normocalcemic. A point that might be helpful is that children with nutritional rickets tend to have a generalized aminoaciduria, whereas the vitamin D dependent type of rickets, which occurs as an autosomal recessive disorder, and the classic X-linked vitamin D resistant rickets do not. In children with the autosomal recessive form, rickets does not develop until 1 year of age and there tends to be a normal serum phosphorus concentration, while a low serum phosphorus level is the hallmark of a patient with the X-linked form.

One difficulty in understanding vitamin D metabolism is that there is no easy method of measuring vitamin D. Only tedious bioassays are available for this purpose. There are many questions that could be answered more easily if we could frequently measure vitamin D. For instance, why are premature infants more susceptible to rickets? Is it because they do not absorb vitamin D as well? Is it because of their small calcium reserve? Is it because they are not yet metabolizing vitamin D completely? These are questions to which we really do not have answers.

In recent years there has been a tremendous

increase in our understanding of vitamin D metabolism. This was initiated by the synthesis of highly radioactive vitamin D and its incubation in various systems. Most of the work has been done in rats and chicks. It was found first that the liver was able to add a hydroxyl group to vitamin D_3, forming 25-hydroxy-cholecalciferol (Figure 7). When this information appeared people became terribly excited because it appeared this might be the answer to vitamin D resistant rickets. Perhaps children with vitamin D resistant rickets lacked the liver enzyme which catalyzes this hydroxylation. This compound was given to patients with vitamin D resistant rickets. It was found that it was effective in vitamin D resistant rickets, but that the dosage required was much higher than the physiological amount. This compound was required in an equivalent dosage to vitamin D to get an equivalent response. These observations excluded the hypothesis. More recently it has been discovered that 25-hydroxy-cholecalciferol is further metabolized in the kidney to the product, 1, 25-dihydroxy-cholecalciferol. This dihydroxy form is extremely active both in stimulating the absorption of calcium from the intestine and in mobilizing calcium from bone. It too has been found not to be the answer to X-linked hypophosphatemic vitamin D-resistant rickets. These new compounds are of enormous theoretical interest. In coming years they are certain to be of clinical importance. Several publications have been included[8-12] in the references that provide detailed information on the metabolism of vitamin D.

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Pancreatic Insufficiency and the Role of Vitamin B_{12} Injections

Patients with pancreatic insufficiency, like patients with other forms of malabsorption, will require replacement therapy. . . . It is clear that patients with pancreatic insufficiency rarely have osteomalacia. Therefore, the requirement for calcium and vitamin D in patients with pancreatic insufficiency is less than in patients with primary malabsorption of the gut. . . . If you can give them the pancreatic enzyme, and they can take it, I would not worry about their vitamin B_{12} malabsorption because they should be absorbing B_{12} normally.

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